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13. ABSTRACT (Maximum 200) In an effort to investigate the etiology responsible for the ongoing chronic fatigue and muscle weakness in veterans with Persian Gulf illness (PG), we are performing a comprehensive evaluation of skeletal muscle in PG veterans with chronic fatigue (CF) and healthy control veterans. Preliminary evaluation of 33 veterans with CF and 19 healthy control veterans shows evidence that muscle function is impaired in veterans with PG illness. Specifically, a significant decrease was found in the mitochondrial ATP producing capacity in veterans with CF compared to healthy veterans, as well as an increased incidence of neuropathic variations. In addition, based on isometric and isokinetic testing in combination with MRI, a pattern of decreased force generating capacity per unit muscle cross-sectional area in veterans with CF emerges. Finally, while the relative fatigability of skeletal muscle in the healthy veterans and veterans with CF is not different, a larger central component was observed in the veterans with CF. Further examination of skeletal muscle focusing on the differentiation between myopathic and neuropathic etiologies is being performed.			
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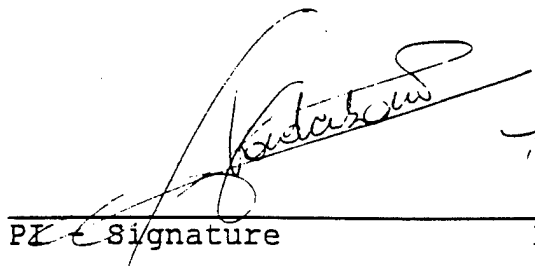
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INTRODUCTION

Since their return from the Persian Gulf region, a large number of veterans have reported health problems. Even though no exact count on the prevalence of symptoms and conditions is available, the VA Registry shows that about 10% of the 697,000 deployed veterans have reported chronic illnesses with a variety of symptoms, including fatigue, muscle and joint pain, headache, rashes and memory loss. In particular, the musculoskeletal system seems to be frequently affected. The most recent DOD report on 18,075 veterans who completed the Comprehensive Clinical Evaluation Program (CCEP) notes that 11% of the veterans report fatigue as their chief complaint, whereas a total of 47% include fatigue as one of their symptoms (1). Muscle pain is reported in 20% of the medically evaluated veterans. Similarly, the VA Registry reports fatigue in 20% of the veterans and muscle and joint pain in 18% of the veterans (2). Even higher incidences of fatigue and muscle pain have been reported by the English (55% tiredness, 35% muscle and joint pain) (3) and the Canadian (86% fatigue, 35% muscle pain) military (4). Thus, muscle appears to be one of the most affected systems in Persian Gulf veterans. In order to investigate the etiology of the muscle related complaints in the Persian Gulf veterans, we put together an interdisciplinary group of scientists with an expertise in Biochemistry, Genetics, Muscle Physiology, Neurology, Physics and Radiology to provide a comprehensive evaluation of skeletal muscle function.

Specifically, the objective of this study is to investigate the etiology responsible for the ongoing chronic fatigue and muscle weakness in veterans with Persian Gulf illness. For this purpose, we evaluate skeletal muscle function of Persian Gulf veterans with severe chronic fatigue and Persian Gulf veterans who were deployed but who have no medical problems. Our primary hypothesis is that muscle function is impaired in Persian Gulf veterans with chronic fatigue. In addition, we hypothesize that the severity of chronic fatigue in this population is related to the degree of muscle dysfunction. To test these hypotheses, a battery of tests are performed. Measurements include ^{31}P -magnetic resonance spectroscopy (MRS), magnetic resonance imaging (MRI), histological and biochemical analyses of muscle biopsies, electrodiagnostic evaluation of motor unit recruitment, muscle enzyme assays, isokinetic and isometric testing, and a functional status questionnaire. Complementary to the functional tests, the subjects are screened for AMP deaminase (AMPD) deficiency.

BODY

A. Subjects

A comprehensive evaluation of skeletal muscle is performed in two subject populations: healthy Persian Gulf veterans and Persian Gulf veterans with chronic fatigue (affected). Veterans with chronic fatigue are defined as those veterans that report ongoing chronic fatigue, with an onset during or shortly after the war, in combination with muscular complaints. Muscular complaints include muscular pain (severity 3 or more on a scale of 5) and/or muscle weakness (severity 3 or more on a scale of 5). Patients are excluded from this study if they present a diagnosable illness. Veterans who have no medical complaints are recruited to serve as controls in this study. The control subjects are matched with the chronic fatigue veterans with regards to age and sex.

To date, 52 subjects have been studied: 33 veterans with chronic fatigue and 19 healthy control veterans. Table 1 provides a summary of the subjects' characteristics. Note that in contrast to the previous report, the difference in age between both populations is minimal.

	Age	Height	Weight
Control	36.4±1.3	68.5±0.4	179.8±2.8
Affected	36.5±1.4	68.5±0.5	181.1±5.3

Table 1. Characteristics of the healthy control Persian Gulf veterans and the Persian Gulf veterans with chronic fatigue (affected).

B. Isometric and isokinetic testing

Because many of the Persian Gulf veterans with chronic fatigue report exercise intolerance, prolonged fatigue after exercise and muscle weakness, we quantitatively assess the muscular strength and endurance of the ankle plantar flexors. Both measurements are performed isokinetically and isometrically. In addition, since maximum voluntary contractions rely heavily on the motivation of the subject and his or her ability to recruit and optimally fire all muscle fibers, measurements are also made using electrical stimulation.

Methods: Muscular strength and endurance of the ankle plantar flexors are tested using a Biodex isokinetic dynamometer. The subjects are seated in upright position (hip angle 90°-100°) with their back tight against the testing chair, which is firmly attached to the dynamometer. The knee joint is stabilized at 0-10° flexion. The foot is set at a 90° angle between the foot and the tibia. The following measurements are made:

- 1) Maximal voluntary isometric strength: defined as the highest torque of three maximal voluntary isometric contractions (5 sec each with 30 sec intervals).
- 2) Electrically evoked peak torque. Surface electrodes (bipolar 4x6inches) are placed over the distal and proximal part of the gastrocnemius. The electrically evoked peak torque is determined using a 100 Hz tetanus (supramaximal intensity; 160ms). The highest peak torque during electrical stimulation is recorded.
- 3) Superimposed peak torque. In order to determine the degree of central inactivation, a tetanus is superimposed during the voluntary MVCs and the increase in peak torque recorded.
- 4) Maximal isokinetic strength is determined at an angular velocity of 60 degrees/sec. The subjects perform five maximal voluntary contractions and the highest peak torque is recorded.
- 5) Peripheral/central fatigue: To discriminate between central and peripheral fatigue, we implement a modified version of the fatigue protocol described by Sharma and Mill (5). The subjects perform a sustained MVC for 90 sec. Prior to and during the sustained contraction, tetanic stimuli (100Hz; supramaximal intensity; 160ms duration) are superimposed at 15 sec intervals to verify that the muscle is fully activated. The peak

torque and the amplitude of the superimposed torque (ST) is recorded at each 15 sec interval. The amplitude of the superimposed torque (ST) is expressed as a proportion of the torque measured during unpotentiated tetani and provides a measure of the decrease in central activation.

6) *Maximal isokinetic endurance* is tested by monitoring the maximal force during 50 repeated isokinetic plantar flexions at 60°/sec. The subjects were instructed to perform repeated plantar flexions with maximal effort. The total work and the relative decline in peak torque during the 50 contractions is recorded.

Results: Based on the total number of subjects that have been tested to date, the plantar flexor strength of Persian Gulf veterans with chronic fatigue is lower than that of healthy veterans (Fig. 1A). An approximate 15-20% difference was found in the isometric and isokinetic strength of healthy and affected Persian Gulf veterans. During superimposed electrical stimulation both populations showed less than 10% central inhibition, indicating that both groups performed maximal voluntary contractions. The superimposed peak torque was $9.6 \pm 1.7\%$ and $7.7 \pm 1.6\%$ in the affected and healthy veterans, respectively.

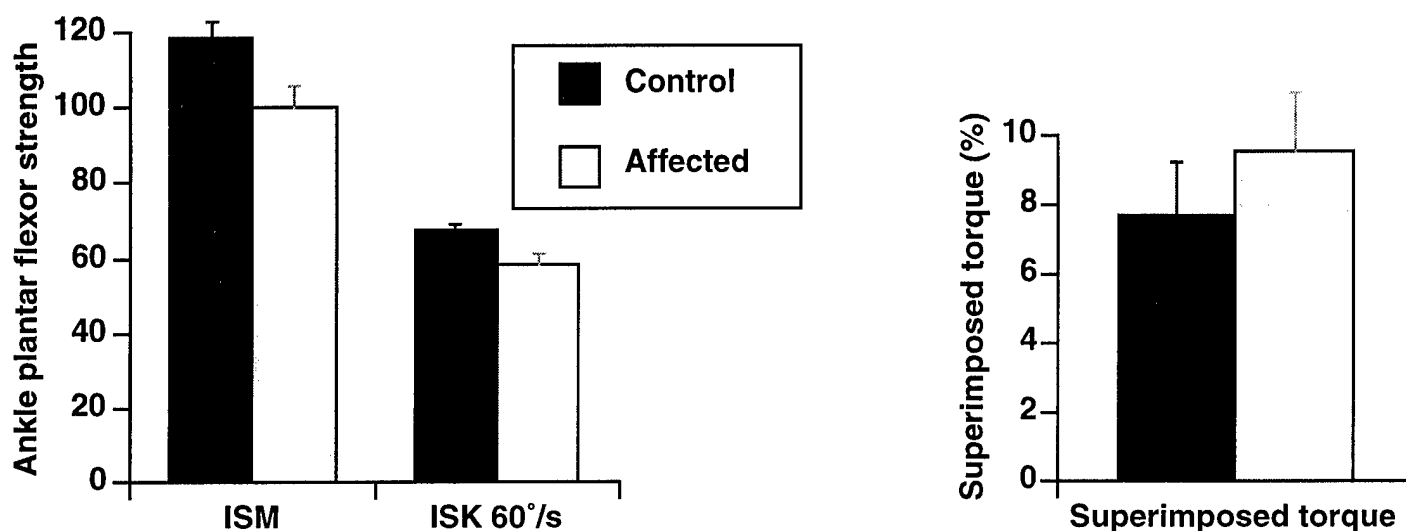


Fig. 1A Peak torque during isometric and isokinetic contractions at 60°/s in healthy control veterans and veterans with chronic fatigue. ISM=isometric; ISK=isokinetic. 1B. Superimposed torque in the healthy control and affected Persian Gulf veterans during maximal voluntary contractions.

These preliminary data confirm the presence of muscle weakness in the Persian Gulf veterans with chronic fatigue. In addition, the superimposed electrical stimulation demonstrates that the difference in muscle strength is not due to a lack of central activation or motivation.

No correction for differences in muscle cross-sectional area (measured via MRI) was performed at this time. However, as reported previously, initial analysis of the MRI images shows that there is no difference in the muscle CSA of both populations. As a result, we anticipate that the force generating capacity per unit muscle cross-sectional area will be smaller in the affected veterans. Based on healthy control civilians we previously determined that the force per unit muscle CSA in healthy ankle plantar flexor muscles equals $3.21 \pm 0.22 \text{ N/cm}^2$. Examination of the muscle specific force in patients with ankle fractures demonstrated that inactivity results in a reduction of the muscle's capacity to generate force per unit muscle CSA, which can be restored with appropriate rehabilitation (Fig. 2A). We anticipate that Persian Gulf veterans with decreased muscle strength will demonstrate a similar decrease in muscle specific force and shift in the force/CSA curve (Fig. 2B). However, whereas the decline in muscle specific force with disuse is primarily related to neurological

adaptations, as demonstrated by a 40-50% increase in superimposed torque, we anticipate that at least part of the muscle dysfunction in the affected Persian Gulf veterans is the result of alterations distal to sarcoplasmic reticulum Ca^{2+} release.

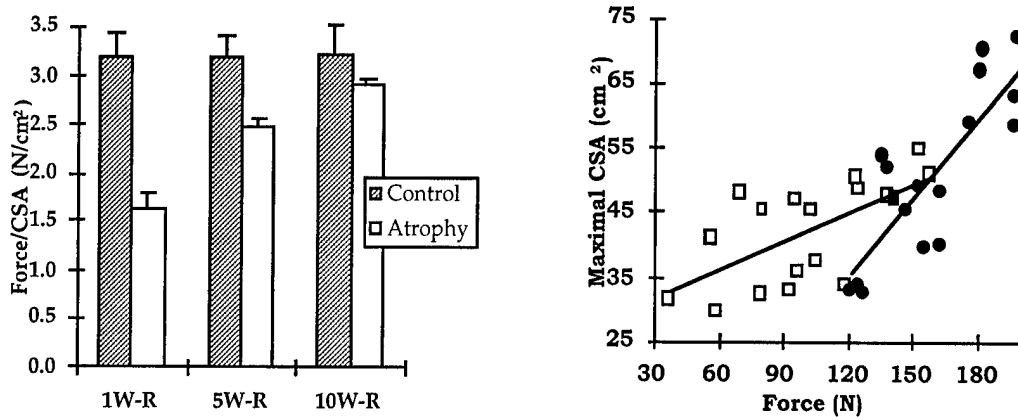


Fig. 2A. Muscle specific force (force/CSA) in healthy control subjects and patients with disuse atrophy following ankle fractures. Note the increase in muscle specific force with rehabilitation. Data were collected after 1 week (1w-R), 5 weeks (5w-R) and 10 weeks (10w-R) of rehabilitation. B. Relationship between muscle force and maximal muscle CSA in control healthy subjects (closed circles) and patients with muscular atrophy (open squares). (Control: $y=0.41x-13.8$, $r^2=0.70$; Atrophy $y=0.15x+27.1$, $r^2=0.43$). We anticipate that Persian Gulf veterans with muscle weakness will demonstrate a decrease in muscle specific force and a left shift in the force/CSA curve.

As shown in Fig. 3A, the relative fatiguability during either the isokinetic or isometric fatigue test was not higher in the sick veterans. The relative fatigue during 50 maximal isokinetic contractions was 37.3 ± 2.5 in the healthy veterans and 34.6 ± 2.7 in the affected veterans. During the isometric test we measured 48.8 ± 1.8 and $46.6 \pm 1.6\%$ fatigue in the healthy and affected veterans, respectively. Of interest to note is that, based on the superimposed electrical stimulation, the affected veterans showed a $44.5 \pm 4.3\%$ central deficit (superimposed torque as a proportion of the unpotentiated torque) during the last 30 sec of the isometric fatigue test, whereas the healthy veterans only demonstrated a $31.7 \pm 2.8\%$ central deficit, indicating a larger central fatigue component in the affected population (Fig. 3B).

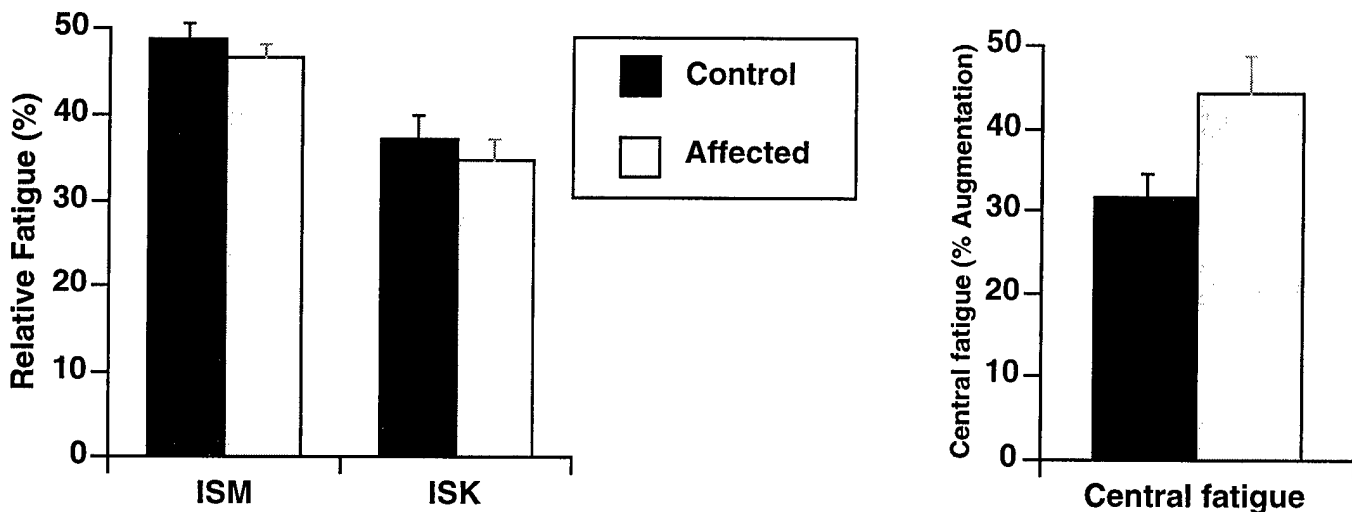


Fig. 3. A. Relative fatiguability in the sick and healthy Persian Gulf veterans measured during an isometric (ISM) and isokinetic (ISK) fatigue test. B. Superimposed torque during the last 30 sec of the isometric fatigue test in control healthy veterans and veterans with chronic fatigue.

C. Functional testing

Methods: To determine the severity of chronic fatigue in the Persian Gulf veterans, we use the functional status questionnaire (FSQ) presented by Jette et al (7) in combination with standard functional tests.

Results: Based on the FSQ and the functional tasks, the overall functional ability of the sick Persian Gulf veterans is lower than that of healthy control veterans (Fig. 4 and 5). The affected veterans showed an overall functional score of $72.9 \pm 2.2\%$ whereas the healthy veterans scored an average of $97.7 \pm 0.6\%$ (questionnaire). During the functional tasks the sick veterans performed on average 8-15% poorer than the healthy veterans.

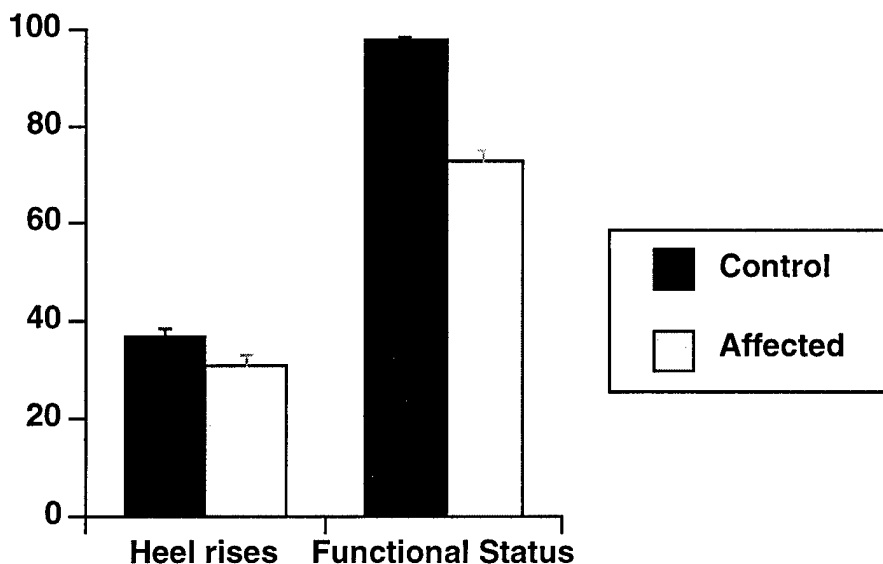


Fig. 4. Results of the functional status questionnaire (FSQ) and the heel rise test in the healthy control veterans and the veterans with chronic fatigue (affected).

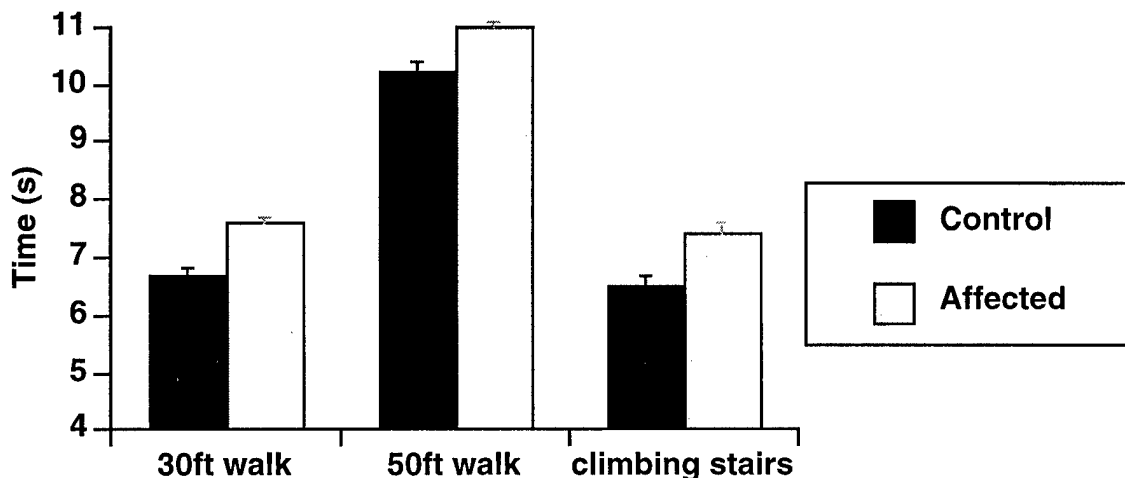


Fig. 5 Results of the timed walks and stairclimbing test in the healthy control veterans and the veterans with chronic fatigue.

D. ^{31}P -Magnetic Resonance Spectroscopy (MRS)

The purpose of these methods is to assess the *in vivo* metabolic characteristics of skeletal muscle in Persian Gulf veterans with severe chronic fatigue. In contrast to the muscle biopsies (see below), ^{31}P -MRS is a noninvasive biochemical sampling technique which provides the opportunity to study muscle metabolism in a fully functioning system. Using this technique, we will measure 1) the basal phosphate content, 2) the metabolic compliance with exercise, 3) the *in vivo* oxidative capacity, 4) the *in vivo* ATPase flux, and 5) the *in vivo* rate of glycolysis.

Methods: All ^{31}P -MRS measurements were performed in a 1 meter, 2.0 Tesla superconducting magnet. The subjects were placed in a supine position inside the magnet with their foot positioned on a pedal ergometer operated against variable air pressure (Fig. 6). Spectra are acquired from the medial gastrocnemius using a 5x4cm oblong surface coil. Spectra are acquired at rest, during voluntary and electrically induced contractions and recovery. For further details see original grant proposal.

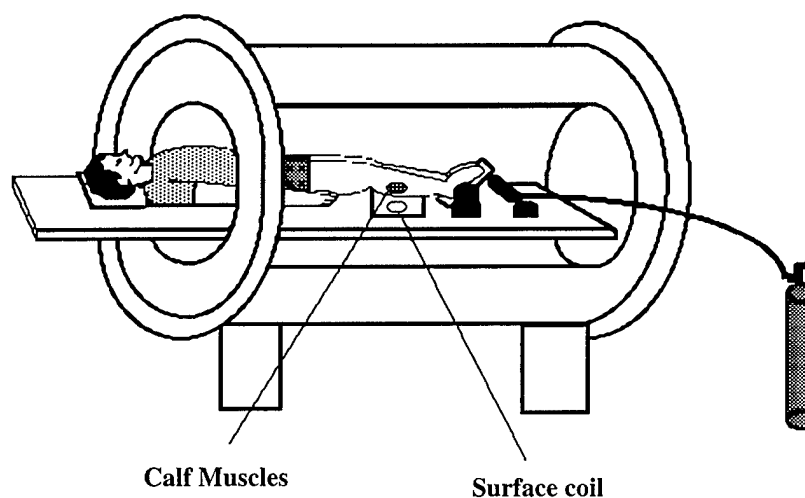


Fig. 6 Graphic display of the experimental set-up for the ^{31}P -MRS measurements.

Using ^{31}P -MRS, we measured the basal content of the phosphate metabolites directly involved in muscle metabolism. Data acquired from the calf muscles of 33 affected Persian Gulf veterans and 25 control healthy veterans showed that the basal Pi concentration in the affected veterans is slightly higher than that of the healthy control veterans, whereas the PCr/Pi ratio is slightly lower. No difference was found in the PCr concentration or intracellular pH at rest.

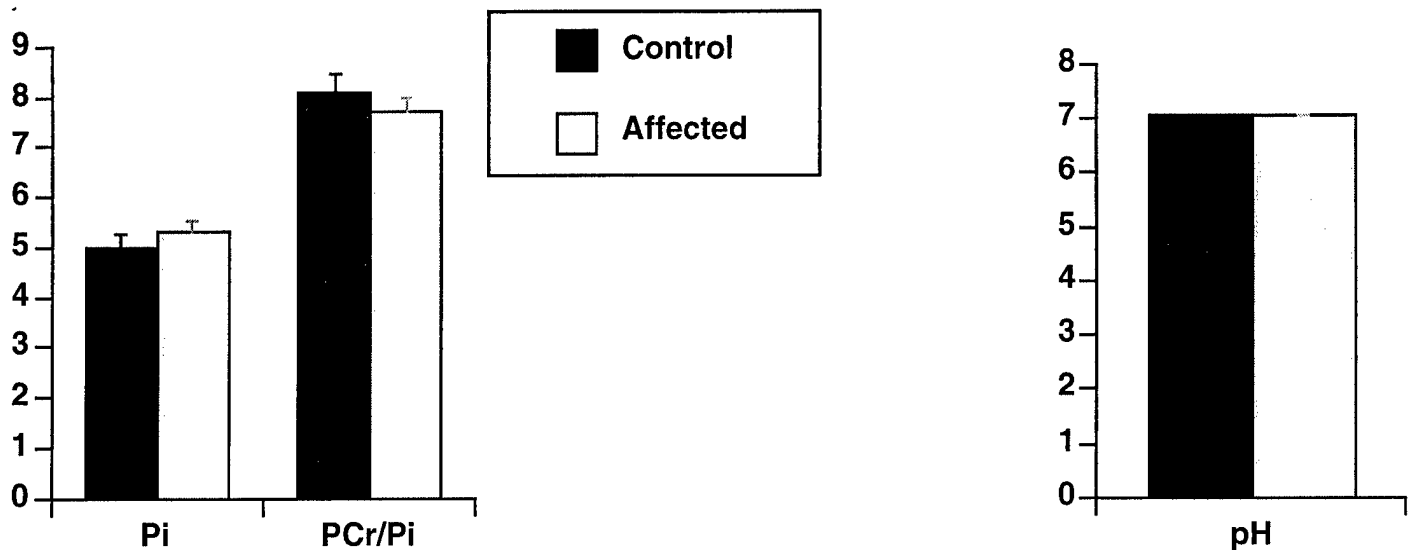


Fig. 7. Basal Pi (mM) concentration, intracellular pH and PCr-to-Pi ratio in skeletal muscle of healthy Persian Gulf veterans and veterans with chronic fatigue.

^{31}P -MRS studies performed during recovery following voluntary exercise and electrically induced contractions indicate that the mitochondrial function of skeletal muscle in Persian Gulf veterans may be impaired. The rate of PCr resynthesis, a measure of the *in vivo* oxidative capacity, was significantly slower in Persian Gulf veterans with chronic fatigue than in healthy control veterans. Of interest to note is that the PCr resynthesis rate of the affected veterans was slower following high repetition rate exercises, steady state exercises as well as following electrical stimulation (Fig. 8). The decrease in the *in vivo* mitochondrial function ranged from 13 to 34%. The largest difference was found following electrical stimulation with a PCr resynthesis rate constant of 1.18 ± 0.17 in the control veterans and 0.79 in the affected veterans.

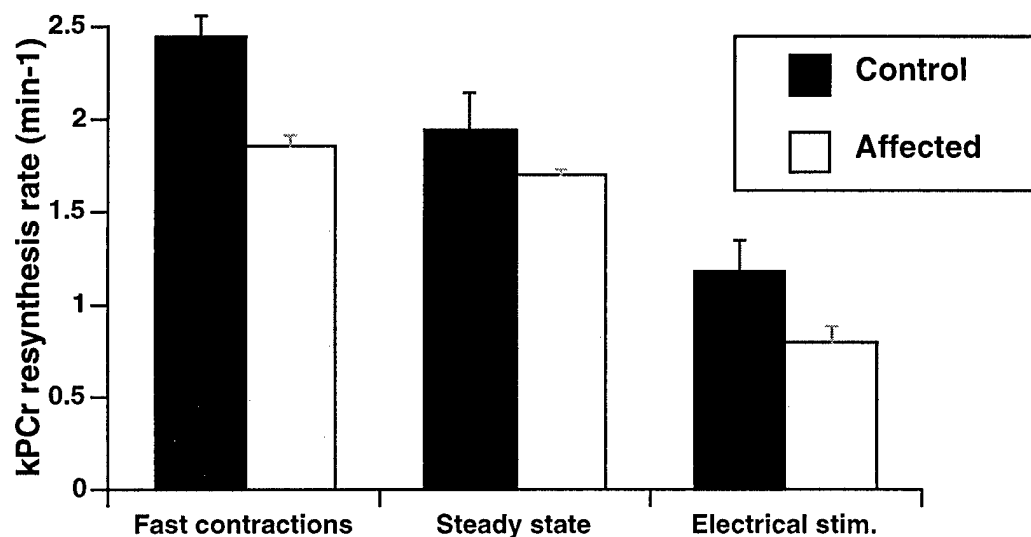


Fig. 8 PCr resynthesis rate in the medial gastrocnemius of healthy control veterans and veterans with chronic fatigue following high repetition rate voluntary exercise, steady state exercise and high frequency electrical stimulation.

The ATPase flux was determined during voluntary “all-out” exercises and high frequency electrical (100Hz, 300msec/700msec) stimulation. Based on both the voluntary exercise and electrical stimulation, no differences exist in the ATPase rates of both populations.

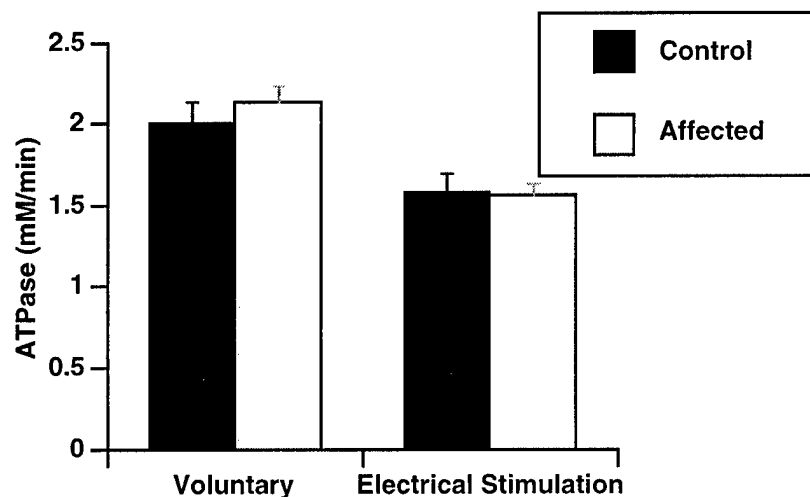


Fig. 9. The maximal ATPase flux during a 60 sec “all-out” exercise and high frequency electrical stimulation in healthy control Persian Gulf veterans and veterans with chronic fatigue.

E. Magnetic Resonance Imaging (MRI)

Methods: All images are collected from the right leg using a 1.5 Tesla magnet and a standard transmit and receive extremity coil. Images are collected from the patella to the calcaneus. 3D-images are acquired using as fast Gradient echo sequence (30 flip angle, TE=9msec, 256x256, FOV=16cm) for volume calculation. In addition, T₂ weighted images are acquired using a TR=2,000ms and TE of 30, 60, 90 and 120msec. During this reporting period we focused our attention on the T₂ analysis.

Results: The mean T₂ values of the calf muscles of 3 healthy control and 9 sick Persian Gulf veterans with chronic fatigue are displayed in Table 2. Note that no difference is observed in the muscle T₂ of both subject populations, indicating the absence of muscle damage or observable muscle inflammation in the affected Persian Gulf veterans.

	Lateral Gastrocnemius	Medial Gastrocnemius	Soleus
Control	29.3±2.8	31.5±3.1	29.6±0.7
Affected	29.0±1.1	28.7±1.0	29.2±0.6

Table 2: The T₂ relaxation rate in the calf muscles of healthy Persian Gulf veterans and veterans with chronic fatigue (affected). Data are expressed in msec.

F. Muscle biopsies

Methods: Muscle biopsies are acquired from the medial gastrocnemius using the needle biopsy technique. In order to increase our biopsy sample size, necessary for multiple analysis, we have implemented the suction

technique as described by Evans et al (8). The procedure is performed using a 60cc syringe with extension tube and a stopcock for multiple sampling. In total, 4 muscle samples are taken: two of the samples are placed in sahnin and prepared for histological examination, 1 sample is mounted in gum tragacanth and frozen in isopentane precooled by liquid nitrogen and used for quantitative biochemical analysis of single fibers, and 1 piece is cut in tiny pieces and prepared for whole muscle homogenate biochemical analysis.

Results: To date, none of the subjects have experienced any adverse affects of the multiple sampling technique or have declined participating in this part of the study. Histological examination of muscle biopsies from 19 subjects: 7 control subjects and 12 affected subjects revealed only minor histological changes in a subpopulation of both control and affected subjects. Histological variations included rare angular fibers, increased central nuclei and increased CT. One of the affected subjects also demonstrated red ragged fibers and signs of inflammation. One of the control subjects demonstrated a possible mitochondrial abnormality.

Quantitative fiber type specific analysis was performed on muscle samples of 9 control subjects. Initial evaluation was performed on the control population in order to compared the obtained numbers with muscle samples from control civilians. However 90% of the samples of both the control and healthy veterans have been stained and are ready for further analysis. Preliminary analysis of the fiber types specific cross-sectional area (CSA), oxidative (SDH) and glycolytic (GPD) enzyme activity is displayed in Table 3. Standard histochemical methods were used to determine the fiber CSA. Microdensitometric techniques were used to determine the fiber type specific SDH and GPD activity.

n=9	Type I	Type IIa	Type IIax
CSA	5953±222	6905±296	6163±418
GPD	31±4	83±9	106±12
SDH	684±69	609±65	670±114

Table 3. Fiber type specific cross-sectional area and muscle enzyme activity in control Persian Gulf veterans. CSAs are expressed as μm^2 ; SDH activity as $\mu\text{mol fumerate/l/min}$. GPD activity as $\mu\text{mol glycerol phosphate/l/min}$.

Consistent with previous studies on the gastrocnemius muscles, the fiber CSA showed the following hierarchy: IIa> IIax>I. As expected, the type I fibers had the highest SDH activity but the lowest GPD activity. The highest GPD activity was found in the Type IIax fibers. These data are consistent with our data acquired in control civilians (SDH between 550 and 837 $\mu\text{mol fumerate/l/min}$; GPD activity between 36 and 92 $\mu\text{mol glycerol phosphate/l/min}$ and fiber CSAs between 5191 and 6784 μm^2).

G. Muscle enzymes

Methods: Blood samples (20cc) are taken from the right arm. 5cc are sent to the lab for alodolase analysis, 5cc is analyzed for CPK and LDH, 2x5cc is send to the genetic diagnostic laboratory for DNA extraction (see below).

Results: The lab work has been performed on 25 veterans with chronic fatigue and 17 healthy control veterans. No difference was found between Persian Gulf veterans with chronic fatigue and healthy control veterans based on mean CPK, alodolase, LDH and CK-MB (Table 4) However, 3/17 healthy veterans and 3/25 veterans demonstrated slightly elevated enzyme activity levels.

	Alodolase	CPK	LDH	CK.MB
Control	5.00±0.52	215.4±62.1	459.2±50.5	3.5±0.4
Affected	5.8±0.2	131.9±17.6	422.8±19.8	0.8±0.1

Table 4. Serum enzyme activity in healthy control veterans and veterans with chronic fatigue.

H. Electrodiagnostic evaluation

Methods: Muscle dysfunction can be related to a neuropathic as well as a myopathic process. To help in the differentiation between both, needle electromyography and nerve conduction studies are performed as well as electrical stimulation (see above). Compound muscle action potentials are elicited from bilateral tibial and peroneal nerves. F-waves are recorded in the standard fashion at distal stimulation sites. Distal latencies, amplitudes and conduction velocities are calculated. Monopolar electromyography is performed on the medial gastrocnemius, lateral gastrocnemius and soleus in order to assess denervation, reinnervation and myopathic changes.

Results: The results of the nerve conduction study are given in Table 5. Based on a comparison between 18 healthy veterans and 25 veterans with chronic fatigue, there was no difference in the mean latencies, amplitudes and conduction velocities of the tibial and peroneal nerve of both populations.

Tibial Nerve

	Conduction velocity (m/s)	F wave	Amplitude distal (mV)	Amplitude proximal (mV)	Latency proximal (ms)	Latency distal (ms)
Control	50.5±0.67	50.2±0.47	10.8±0.8	9.98±0.75	13.1±0.22	4.9±0.12
Affected	51.37±0.59	49.66±0.58	11.9±0.71	11.4±0.71	12.7±0.21	4.9±0.1

Table 5. A. Results of the electrodiagnostic test performed on the tibial nerve of healthy and sick PG veterans.

Peroneal Nerve

	Conduction velocity (m/s)	F wave	Amplitude distal (mV)	Amplitude proximal (mV)	Latency proximal (ms)	Latency distal (ms)
Control	47.8±0.44	50.5±0.64	4.95±0.25	4.65±0.24	10.9±0.18	4.98±0.15
Affected	48.08±0.54	49.25±0.51	5.47±0.32	5.10±0.29	10.98±0.14	4.49±0.08

Table 5. B. Results of the electrodiagnostic test performed on the peroneal nerve of healthy and sick PG veterans.

In contrast, as shown in Table 6, using monopolar electromyography, significant differences were observed between the control healthy veterans and veterans with chronic fatigue. In particular, the incidence of polyphasic motor unit potentials, increased firing rates and decreased motor unit recruitment was higher in the affected population compared to the control population. Specifically, 6/25 affected veterans demonstrated increased polyphasic motor unit potentials with increased amplitude and duration; 2/25 showed increased firing rates and 1/25 showed spontaneous activity at rest. In addition, a total of 12/25 subjects demonstrated

decreased motor unit recruitment. In contrast, none of the control patients demonstrated any abnormality on EMG evaluation.

	Spontaneous activity	Increased polyphasic potentials	Decreased recruitment	Increased firing rates
Control	0/18	0/18	0/18	0/18
Affected	1/25	6/25	12/25	2/25

Table 6. Results of the monopolar EMG performed on the calf muscles of healthy veterans and veterans with chronic fatigue.

I. Genetic screening

As a complementary project to the functional studies to be performed in these patients, peripheral blood samples are collected for isolation of DNA. The purpose of isolating DNA is to screen for genetic defects, or polymorphisms, which may have predisposed individuals to develop symptoms following military service in the Persian Gulf. Although many genetic defects, or polymorphisms, may be responsible for the pathologic consequences experienced by the Persian Gulf veterans, and many could be screened with the DNA samples obtained through this study, we will initially only screen for AMP deaminase (AMPD) deficiency.

Results: To date all of the samples have been labeled with random numbers not corresponding to the volunteer study number. DNA of 22 affected and 13 healthy control veterans has been isolated and analyzed for AMP deaminase. In the control population 11/13 samples were negative and 2/13 heterozygous. In the affected group similar results were found (2/25 heterozygous, 23/25 negative).

J. Recommendations in relation to statement of work outlined in the proposal

The second year of study has been completed. We are very pleased with all aspects of the study. Progress has been made in all areas, including the genetic screening for polymorphism. In contrast to the previous reporting period, the subjects are now matched in age, with a mean age of 36.4 ± 1.3 in the control population and 36.5 ± 1.4 in the affected population.

CONCLUSIONS

In an effort to investigate the etiology responsible for the ongoing chronic fatigue and muscle weakness in veterans with Persian Gulf illness, we are performing a comprehensive evaluation of skeletal muscle in Persian Gulf veterans with chronic fatigue and healthy control veterans. To date, 52 Persian Gulf veterans have been studied: 33 veterans with chronic fatigue and 19 healthy control veterans. Even though the data are preliminary, they do indicate that muscular abnormalities may contribute to the symptom profile of Persian Gulf veterans. The most important finding in this study is a 15-34% decrease in the mitochondrial ATP-producing capacity in Gulf veterans with chronic fatigue compared to health control veterans and a higher incidence of neurological abnormalities. Neurological variations include increased firing rates, increased incidences of polyphasic motor unit potentials and spontaneous activity at rest. In addition, isokinetic and isometric testing of the ankle plantar flexors shows a 15-20% difference in the muscular strength of Persian Gulf veterans with chronic fatigue and healthy control veterans. Since initial analysis of MRI images has shown that the muscle CSA is not different between both populations, we anticipate that the Persian Gulf veterans with chronic fatigue will demonstrate a decreased force generating capacity per unit muscle cross-sectional area. Superimposed electrical stimulation during maximal voluntary contractions indicates that the decrease in force generating capacity in the Persian Gulf veterans is caused by peripheral changes and not central deficits. In contrast, superimposed electrical stimulation during a 90 sec fatigue tests demonstrates a larger central fatigue component in the veterans with chronic fatigue. Finally, standard clinical blood work and histological evaluation of muscle biopsies shows no indications of a higher incidence of muscle damage in the Persian Gulf veterans with chronic fatigue. Even though these data show clear evidence of an increased incidence of muscle dysfunction in Persian Gulf veterans with chronic fatigue, further careful examination of skeletal muscle focusing on the differentiation between neuropathic and myopathic etiologies is needed.

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